September 7, 2004

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Cc: Dr. Gary Benzion, USPTO
Dr. Mai Nguyen

RE: Patent Application # 09/938,013

This is to confirm our telephone conferencing appointment with you, Dr. Benzion, Mai Nguyen (tel. 760/438-5083) and Khue Nguyen (tel. 619/543-3623) on Sep. 9, 2004, at 12 noon Eastern time (9:00 am California time).

To facilitate our conferencing, please find attached a draft of some of the main points that I hope could be addressed.

Total fax pages: 3

Following are some of the points and issues I hope you would clarify and address for me.

A/ I do not understand why you still maintain the issue of new matter in the last Office communication (6/4/2004) while you had already accepted my clarification that there is no new matter as per my phone discussion with you on 1/20/2004 and following my 12/9/2003 FAX. On July 15, 2003 you said that you would not pursue the examination of the application unless the issue of new matter is resolved; the fact of the matter is that you have accepted that there is no new matter by the very fact that you have continued to examine my application.

B/ After my clarification for you regarding the difference between's Jong's method and my method (refer to 5/24/2004 FAX and 5/26/2004 phone conferencing, see 5/28/2004 FAX) you accepted that my work is novel. During the phone conferencing, you talked about the known techniques that can be applied to all kinds of disease; I pointed out that if that is the case, then we would have found the cure all the diseases of the world; so you then agreed to focus your consideration of the application as applied to the SMA disease. I do not understand why, in the 6/4/2004 Office communication , you however talked about the various techniques used for various purposes but not specifically applied for SMA diagnostic purpose.

C/ It is not clear as to why sometimes you stated that Jong's method is semi-quantitative (pages 11, 14, 16 of 6/4/2004 Office communication) and sometimes you stated that Jong's method is quantitative by stating that "the ratio is a quantitative method" (page 11 of 6/4/2004 Office communication), and by saying that "Jong teaches performing quantitative analysis by determining the ratio of exon 7..." (page 15 of 6/4/2004 Office communication) which is a misunderstanding on your part because the ratio has nothing to do with characterizing the type of method used in order to get the results of the experiments; the research method used can be qualitative, semi-quantitative or quantitative. In fact, the ratio is a means to correct the fluctuations of the PCR reaction rate to compare the results from one sample to another. In each sample, each result obtained from the PCR product to amplify exon 7 of the SMN gene is compared to the obtained result from the positive internal control, i.e., used as an internal referent, in order to estimate the number of transcripts containing exon 7 (or lacking exon 7). For example, in sample 1, the PCR reaction may give the amplification number 20 times and the internal referent may give the number 10 times; in sample 2, the PCR reaction may give the amplification number 10 times, and the internal referent may give the number 5 times. Researchers do not use the raw value of 20 in sample 1 nor the raw value of 10 in sample 2 to make comparisons because it gives inaccurate information (due to PCR reaction rate varying from one sample to another); researchers use the ratio 20/10 in sample 1 to compare with 10/5 in sample 2. Moreover, the more stable the PCR reaction rate of the internal referent is across samples, the more accurate the comparison would be possible.

In Jong et al.'s article, these researchers specified that they used the semi-quantitative method based on the intensity of the band of the PCR product, i.e., looking at the darker or lighter shade of the bands in order to estimate the results obtained; then, from the obtained estimated results, Jong et al. performed a ratio to make the comparisons.

In brief, it is unclear as to what your interpretation of the cited U.S.C. 103 (a) clause is and how you connect that to my specific case; you indicated that any ordinary artisan would have done this and that, while the fact of the matter is that no one before the date of this application has thought of nor successfully combined the various techniques to develop the quantitative method for molecular diagnosis of SMA at the mRNA level; no one before my application has used probes to detect SMA at the mRNA level. It is unclear as to how U.S.C. 103 (a) is interpreted and applied while you acknowledged that the development of a quantitative method would be an improvement of Jong's semi-quantitative method (page 16 of the 6/4/2004 Office communication).